On Altered Patterns of Brain Activation in At-Risk Adolescents and Young Adults

In an article in this issue, Yaakub et al. (1) report on a functional MRI (fMRI) study of patterns of brain activity in 60 adolescents and young adults at risk for psychosis and 38 healthy comparison subjects, using a working memory task that included separate maintenance and manipulation conditions. The at-risk group included patients with a first-degree family history of psychosis; an attenuated psychosis subgroup with subthreshold psychotic symptoms; and a subgroup with brief, limited intermittent psychotic symptoms. Analyses of the imaging data focused on two networks: the lateral prefrontal and parietal cortices, which are specifically involved in working memory; and the default mode network, which is often deactivated during engagement in a specific cognitive task. Although the two groups were comparable in behavioral performance on the working memory task, they showed different patterns of brain activation. Regardless of task condition, the at-risk group showed less activation than the healthy group in the left anterior insula and posterior cingulate cortex. During the manipulation condition, at-risk individuals showed greater activation in the right dorsolateral prefrontal cortex and greater deactivation within the default mode network than healthy subjects. The primary conclusion was that altered patterns of brain activation may indicate elements of reduced function as well as compensation in individuals at risk for psychosis. These findings were also viewed as being potentially useful for detecting early brain changes to facilitate treatment of at-risk persons.

The Yaakub et al. study has several strengths, such as the large and primarily antipsychotic-naive at-risk sample, and the findings are thought provoking. The finding of generally decreased insula function is intriguing but somewhat difficult to contextualize. The anterior insula has been shown to be involved in error processing and in task set control functions, which may be important for a broad range of cognitive functions (2–4). However, the anterior insula does not play a key role in major models of working memory, and insular abnormalities have not typically been observed in fMRI studies of working memory in individuals diagnosed with or at risk for schizophrenia. Thus, we focus our comments on the findings concerning increased activation of the dorsolateral prefrontal cortex during working memory manipulation given its central role in models of working memory and supporting literature in imaging studies. Yaakub et al. conclude that increased activation of this region during working memory manipulation is a compensatory mechanism in at-risk individuals. In the text that follows, we discuss this conclusion in the context of the larger body of literature on fMRI studies of working memory in various types of at-risk samples and healthy adults, and we consider the implications of Yaakub and colleagues' findings for early intervention in at-risk individuals.

Based on the findings from 17 fMRI studies of working memory-related paradigms in at-risk samples that we identified (Table 1), the literature appears decidedly mixed concerning prefrontal cortex activation. We found four studies indicating selected areas of hyperactivation, six indicating selected areas of hypoactivation, three indicating mixed activation differences (e.g., some areas with hyperactivation, others with

hypoactivation, or areas with different patterns as a function of stimulus type), and four finding no differential activation. Thus, prefrontal cortex hyperactivation, either alone or in combination with hypoactivation, was seen in 41% of studies of at-risk samples.

In healthy adults, dorsolateral prefrontal cortex activity increases with increasing memory load until working memory capacity is exceeded, and then it decreases. It has been hypothesized that a similar process of increased activity with increasing memory load may take place in individuals with schizophrenia, but that decreases in activation occur earlier under conditions of lower memory load because of reduced working memory capacity (5–7). Interestingly, some studies show hyperactivation in the dorsolateral prefrontal cortex during working memory manipulation tasks, co-occurring with hypoactivation in other dorsolateral prefrontal cortex regions when individuals with chronic schizophrenia are compared with healthy subjects. The pattern differences appear to depend on performance, with hyperactivation associated with preserved performance and hypoactivation associated with impaired performance (8). Furthermore, the regions of the dorsolateral prefrontal cortex showing hyperactivation tend to be either more anterior (on the right) or more inferior (on the left) and appear to be distinct from the regions showing hypoactivation (9). Such a pattern may suggest a compensatory role for certain regions of this structure when other regions are not able to function properly. Although altered patterns of activation are occasionally observed in samples of patients with chronic schizophrenia, meta-analyses of working memory and/or other cognitive control paradigms in schizophrenia have converged on hypoactivation of the dorsolateral prefrontal cortex as the most common finding (10, 11).

The hyperactivation observed in the Yaakub et al. study could reflect compensatory changes in brain activity, at least for a subgroup of at-risk individuals.

If hyperactivation served a compensatory role during working memory conditions that are within an individual's working memory capacity, then we might expect to observe this phenomenon more frequently in at-risk samples than in chronic samples, because in the former, working memory capacity is greater, performance is more intact, symptoms are at subclinical levels, and brain changes that can accommodate early cognitive impairment are perhaps more fluid. Based on our review of at-risk studies, hyperactivation of the dorsolateral prefrontal cortex appears to be more common in at-risk than chronic samples (8, 11), although the data are clearly mixed. Hence, we generally agree that the hyperactivation observed in the Yaakub et al. study could reflect compensatory changes in brain activity, at least for a subgroup of at-risk individuals.

As Yaakub et al. note, hyperactivation may suggest an adaptive response to the at-risk mental state. The increased engagement and activation of functionally capable cognitive processing resources may enable the individual in the at-risk mental state to perform cognitive tasks requiring the maintenance and manipulation of information at levels comparable to healthy subjects. Can we take this finding a step further? For a subgroup of at-risk individuals, might compensatory brain activity serve a protective function against clinical deterioration or, perhaps, conversion to a psychotic disorder? Alternatively, hyperactivation of the dorsolateral prefrontal cortex, albeit adaptive, may signal early brain compromise that eventually leads to hypoactivation and cognitive decline as the illness progresses and neural capacity declines. Given the ages common to individuals in the at-risk

TABLE 1. fMRI Studies of Working Memory in At-Risk Samples[a]

Study Type and Reference	Sample	Task and Performance in At-Risk Compared With Control Groups	Lateral PFC Activation in At-Risk Compared With Control Groups
Clinical at-risk mental state (ARMS) studies			
Yaakub et al. (in this issue of the *Journal*)	60 ARMS patients (1 previously took antipsychotic); 38 healthy controls; mean ages, 21–23 years	Maintenance and manipulation task. Participants excluded if <75% correct, therefore no group differences	↑ Right inferior frontal gyrus, right frontal eye field, left precentral gyrus during manipulation (whole-brain analysis). ↑ Right posterior DLPFC during manipulation (subsequent region-of-interest analysis)
Smieskova et al. (Hum Brain Mapp 2012; 33: 2281–2294)	17 ARMS patients, *short-term* (average, 3 months after ascertainment);16 ARMS patients, *long-term* (average, 4.5 years after ascertainment) (2 ARMS patients medicated at time of scanning; 1 previously medicated); 20 healthy controls; 21 first-episode psychosis patients; mean ages, 25–29 years	N-back task (0, 1, 2 conditions). No group differences in accuracy; reaction time slower in short-term ARMS patients compared with healthy controls and long-term ARMS patients	*Short-term* ARMS patients: ↓ left superior frontal gyrus. *Long-term* ARMS patients: no group differences (data analyzed using a mask based on 2-back performance across all groups)
Fusar-Poli et al. (J Psychiatr Res 2011; 45:190–198)	15 ARMS patients (baseline and 12-month follow-up assessments; antipsychotic naive at baseline); 15 healthy controls (baseline assessments only); mean ages, 24–25 years (partly overlapping sample with Fusar-Poli et al., 2010)	N-back task (0, 1, 2 conditions). Baseline: trend toward lower accuracy but no reaction time difference. Follow-up: ARMS patients compared with healthy controls at baseline: no group differences	↓ Left middle frontal gyrus at baseline; no group differences for ARMS patients follow-up data compared with control group baseline data (whole-brain analysis)
Fusar-Poli et al. (Arch Gen Psychiatry 2010; 67:683–691)	20 ARMS patients (antipsychotic naive); 14 healthy controls; mean ages, 25–27 years	N-back task (0, 1, 2 conditions). No group differences	↓ Left middle frontal gyrus (whole-brain analysis)
Broome et al. (Br J Psychiatry 2009; 194:25–33)	17 ARMS patients (antipsychotic naive); 10 first-episode psychosis patients; 15 healthy controls; mean ages, 24–26 years	N-back task (0, 1, 2 conditions). No group differences	↓ Left inferior frontal gyrus, right medial/superior frontal gyrus during 2-back. No group differences during 1-back (whole-brain analyses)
Crossley et al. (Hum Brain Mapp 2009; 302:4129–4137)	16 ARMS patients (antipsychotic naive); 10 first-episode psychosis patients; 13 healthy controls; mean ages not reported	N-back task (0, 1, 2 conditions). No group differences in errors, reaction time not reported	No group differences (whole-brain analysis)
Twin studies			
Karlsgodt et al. (Schizophr Res 2007; 89:191–197)	10 unaffected co-twins; 13 control twins; 8 schizophrenia probands; mean ages, 50–52 years	Modified Sternberg recognition task with 3, 5, 7, 9 letters. No group differences; trend for probands < co-twins < controls	No group differences (whole-brain and region-of-interest analyses)
Unaffected relative studies			
Bakshi et al. (J Psychiatr Res 2011; 45:1067–1076)	19 offspring; 25 healthy controls; mean ages, 14–15 years	N-back task (0,1,2 conditions). No accuracy differences; offspring had faster reaction times than controls	No group differences (region-of-interest analyses)

continued

TABLE 1. fMRI Studies of Working Memory in At-Risk Samples[a] (*continued*)

Study Type and Reference	Sample	Task and Performance in At-Risk Compared With Control Groups	Lateral PFC Activation in At-Risk Compared With Control Groups
Karch et al. (J Psychiatric Res 2009; 43:1185–1194)	11 first-degree relatives; 11 healthy controls; 11 schizophrenia patients; mean ages, 33–34 years	N-back task (0–3 conditions). Relatives fell intermediate between healthy controls and schizophrenia patients for accuracy and reaction time; unclear if significantly different from healthy controls	↓ Left and right superior and middle frontal gyrus; left middle/ interior frontal gyrus (whole-brain analysis)
Meda et al. (Schizophr Res 2008; 104:85–95)	23 first-degree relatives; 43 healthy controls; mean ages, 42–51 years	Modified Sternberg task (sizes 4, 5, 6 conditions) with encoding and response selection phases. No group differences for accuracy; relatives had slower reaction times than healthy controls	↓ Middle and inferior frontal during encoding phase. ↓ Superior frontal during response selection phase (region-of-interest analyses)
Seidman et al. (Neuropsychology 2007; 21:599–610)	12 first-degree relatives; 13 healthy controls; mean ages, 35–37 years	Three versions of auditory CPT: baseline vigilance QA task; WM–60% INT; high load WM task WM–100% INT. No significant performance differences	No group differences (region-of-interest analyses)
Brahmbhatt et al. (Schizophr Res 2006; 87: 191–204)	18 siblings; 72 healthy controls; 19 schizophrenia patients; mean ages, 20–22 years	Word and face N-back task (0 and 2 conditions). Decreased accuracy on "lure" trials	↑ Right PFC for words. ↓ Right PFC for faces (whole-brain analyses)
Seidman et al. (Schizophr Res 2006; 85:58–72)	21 first-degree relatives; 24 healthy controls; mean ages, 18–20 years	N-back (2-back) task. No group differences	↑ Right DLPFC (region-of-interest analysis)
Thermenos et al. (Biol Psychiatry 2004; 55:490–500)	12 first-degree relatives; 12 healthy controls; mean ages, 32–36 years	Two versions of auditory CPT: baseline vigilance QA task; high load WM task Q3A-INT. No group differences on QA task; relatives worse on Q3A-INT and trend toward slower reaction time	↑ Left DLPFC (region-of-interest analysis)
Callicott et al. (Am J Psychiatry 2003; 160: 709–719)	*Study 1:* 23 unaffected siblings; 18 healthy controls. *Study 2:* 25 unaffected siblings; 15 healthy controls. Mean ages, 28–37 years	N-back task (0,1,2 conditions). No group differences	*Study 1:* ↑ Right DLPFC, left and right inferior frontal gyrus. *Study 2:* ↑ Right DLPFC, right inferior frontal gyrus (whole-brain analyses)
Keshavan et al. (Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 1143–1149)	4 offspring; 4 healthy controls; mean ages, 12 years	Visually guided saccade task and memory-guided saccade task. No group differences	↓ Left and right DLPFC, right middle frontal (whole-brain analyses)
Clinical at-risk plus unaffected relative studies			
Choi et al. (Schizophrenia Bull 2012; 38:1189–1199)	21 ultra-high-risk patients (5 taking antipsychotics); 17 first-degree relatives; 15 schizophrenia patients; 16 healthy controls; mean ages, 21–23 years	Spatial delayed response task, including encoding, maintenance, retrieval stages. No differences between ultra-high-risk patients and healthy controls; relatives compared with healthy controls: no accuracy differences but relatives had decreased reaction time	*Ultra-high-risk group:* Encoding: ↓ Right DLPFC; maintenance: no group differences; retrieval: ↓ right ventrolateral PFC, ↑ left DLPFC. *Relatives group:* Encoding: ↑ Right DLPFC; maintenance: no group differences; retrieval: no group differences (whole-brain analyses)

[a] ARMS=at-risk mental states; CPT=Continuous Performance Task; DLPFC=dorsolateral prefrontal cortex; PFC=prefrontal cortex.

mental state, consideration should be given to how these patterns of activation occur alongside the dynamic changes occurring in these brain regions during normal maturation. The few existing studies in this area have provided mixed results (12–14). Additional longitudinal studies of at-risk individuals are needed to examine adaptive versus abnormal trajectories of neurodevelopment. Furthermore, given the testable hypothesis that hypo- versus hyperactivation might be driven in part by memory load and performance, it would be useful for future studies to embrace a set of standardized paradigms that manipulate processing load and performance levels. Fortunately, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) consortium is providing much-needed recommendations for paradigms in this area (15).

What do these findings implicate for the treatment of at-risk individuals? Yaakub et al. appear to be suggesting that brain imaging may be able to detect relevant brain markers for treatment that performance measures cannot identify. This might be a useful mechanism by which to guide clinical trials research, but it is not practical for clinical practice unless much stronger convergence is found. Even with stronger convergence, the issue of early intervention for at-risk individuals raises bioethical concerns that require careful consideration, particularly given the fact that the majority of at-risk individuals never convert to a psychotic disorder. Thus, we concur with the position suggested by others that clinicians focus on treating the broad syndrome of early mental distress, including nonspecific psychotic experiences, anxiety, depression, and fluctuations in mood that frequently occur in individuals during the period of risk for illness onset, rather than treating a high-risk syndrome (16).

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